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(54) Title: COMPOUNDS AND METHODS

(57) Abstract: Compounds of this invention are non-peptide, reversible inhibitors of type 2 methionine aminopeptidase, useful in treating conditions mediated by angiogenesis, such as cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity.

COMPOUNDS AND METHODS

FIELD OF THE INVENTION

Compounds of this invention are non-peptide, reversible inhibitors of type 2 methionine aminopeptidase, useful in treating conditions mediated by angiogenesis, such as cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity.

BACKGROUND OF THE INVENTION

In 1974, Folkman proposed that for tumors to grow beyond a critical size and to spread to form metastases, they must recruit endothelial cells from the surrounding stroma to form their own endogenous microcirculation in a process termed angiogenesis (Folkman J. (1974) *Adv Cancer Res. 19*; 331). The new blood vessels induced by tumor cells as their life-line of oxygen and nutrients also provide exits for cancer cells to spread to other parts of the body. Inhibition of this process has been shown to effectively stop the proliferation and metastasis of solid tumors. A drug that specifically inhibits this process is known as an angiogenesis inhibitor.

Having emerged as a promising new strategy for the treatment of cancer, the anti-angiogenesis therapy ("indirect attack") has several advantages over the "direct attack" strategies. All the "direct attack" approaches such as using DNA damaging drugs, antimetabolites, attacking the RAS pathway, restoring p53, activating death programs, using aggressive T-cells, injecting monoclonal antibodies and inhibiting telomerase, etc., inevitably result in the selection of resistant tumor cells. Targeting the endothelial compartment of tumors as in the "indirect attack", however, should avoid the resistance problem because endothelial cells do not exhibit the same degree of genomic instability as tumor cells. Moreover, anti-angiogenic therapy generally has low toxicity due to the fact that normal endothelial cells are relatively quiescent in the body and exhibit an extremely long turnover. Finally since the "indirect attack" and "direct attack" target different cell types, there is a great potential for a more effective combination therapy.

More than 300 angiogenesis inhibitors have been discovered, of which about 31 agents are currently being tested in human trials in treatment of cancers (Thompson, et al., (1999) *J Pathol 187*, 503). TNP-470, a semisynthetic derivative of fumagillin of *Aspergillus fuigatus*, is among the most potent inhibitors of angiogenesis. It acts by directly inhibiting endothelial cell growth and migration *in vitro and in vivo* (Ingber et al. (1990) *Nature 348*, 555). Fumagillin and TNP-470, have been shown to inhibit type 2 methionine aminopeptidase (hereinafter MetAP2) by irreversibly modifying its active

site. The biochemical activity of fumagillin analogs has been shown to correlate to their inhibitory effect on the proliferation of human umbillical vein endothelial cells (HUVEC). Although the mechanism of the selective action of fumagillin and related compounds on MetAP2-mediated endothelial cell cytostatic effect has not yet been established, possible roles of MetAP2 in cell proliferation have been suggested.

First, hMetAP-2-catalyzed cleavage of the initiator methionine of proteins could be essential for releasing many proteins that, after myristoylation, function as important signaling cellular factors involved in cell proliferation. Proteins known to be myristoylated include the src family tyrosine kinases, the small GTPase ARF, the HIV protein nef and the α subunit of heterotrimeric G proteins. A recently published study has shown that the myristoylation of nitric oxide synthase, a membrane protein involved in cell apoptosis, was blocked by fumagillin (Yoshida, et al. (1998) *Cancer Res. 58(16)*, 3751). This is proposed to be an indirect outcome of inhibition of MetAP2-catalyzed release of the glycine-terminal myristoylation substrate. Alternatively, MetAP enzymes are known to be important to the stability of proteins *in vivo* according to the "N-end rule" which suggests increased stability of methionine-cleaved proteins relative to their N-terminal methionine precursors (Varshavsky, A (1996) *Proc. Natl. Acad. Sci. U.S.A 93*, 12142). Inhibition of hMetAP2 could result in abnormal presence or absence of some cellular proteins critical to the cell cycle.

Methionine aminopeptidases (MetAP) are ubiquitously distributed in all living organisms. They catalyze the removal of the initiator methionine from newly translated polypeptides using divalent metal ions as cofactors. Two distantly related MetAP enzymes, type 1 and type 2, are found in eukaryotes, which at least in yeast, are both required for normal growth; whereas only one single MetAP is found in eubacteria (type 1) and archaebacteria (type 2). The N-terminal extension region distinguishes the methionine aminopeptidases in eukaryotes from those in procaryotes. A 64-amino acid sequence insertion (from residues 381 to 444 in hMetAP2) in the catalytic C-terminal domain distinguishes the MetAP-2 family from the MetAP-1 family. Despite the difference in the gene structure, all MetAP enzymes appear to share a highly conserved catalytic scaffold termed "pita-bread" fold (Bazan, et al. (1994) *Proc. Natl. Acad. Sci. U.S.A. 91*, 2473), which contains six strictly conserved residues implicated in the coordination of the metal cofactors.

Mammalian type 2 methionine aminopeptidase has been identified as a bifunctional protein implicated by its ability to catalyze the cleavage of N-terminal methionine from nascent polypeptides (Bradshaw, et al (1998) *Trends Biochem. Sci. 23*, 263) and to associate with eukaryotic initiation factor 2α (eIF-2α) to prevent its phosphorylation (Ray, et al. (1992) *Proc. Natl. Acad. Sci. U.S.A. 89*, 539). Both the

genes of human and rat MetAP2 were cloned and have shown 92% sequence identity (Wu,. et al. (1993) *J Biol. Chem. 268*, 10796; Li, X. & Chang, Y.-H. (1996) *Biochem. & Biophys. Res. Comm. 227*, 152). The N-terminal extension in these enzymes is highly charged and consists of two basic polylysine blocks and one aspartic acid block, which has been speculated to be involved in the binding of eIF-2α (Gupta, et al. (1993) in *Translational Regulation of Gene Expression 2* (Ilan, J., Ed.), pp405-431, Plenum Press, New York).

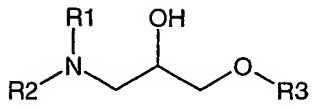
The anti-angiogenic compounds, fumagillin and its analogs, have been shown to specifically block the exo-aminopeptidase activity of hMetAP2 without interfering with the formation of the hMetAP2 : eIF2α complex (Griffith, et al., (1997) *Chem. Biol. 4*, 461; Sin, et al. (1997) *Proc. Natl. Acad. Sci. U.S.A. 94*, 6099). Fumagillin and its analogs inactivate the enzymatic activity of hMetAP2 with a high specificity, which is underscored by the lack of effect of these compounds on the closely related type 1 methionine aminopeptidase (MetAP1) both *in vitro* and *in vivo* in yeast (Griffith, et al., (1997) *Chem. Biol. 4*, 461; Sin, et al. (1997) *Proc.Natl.Acad.Sci. U.S.A. 94*, 6099). The extremely high potency (IC50 < 1 nM) of these inhibitors appears to be due to the irreversible modification of the active site residue, His231, of hMetAP2 (Liu, et al. (1998) *Science 282*, 1324). Disturbance of MetAP2 activity *in vivo* impairs the normal growth of yeast (Griffith, et al., (1997) *Chem. Biol. 4*, 461; Sin, et al. (1997) *Proc. Natl. Acad. Sci. U.S.A. 94*, 6099; In-house data) as well as Drosophila (Cutforth & Gaul (1999) *Mech. Dev. 82*, 23). Most significantly, there appears to be a clear correlation between the inhibition effect of fumagillin related compounds against the enzymatic activity of hMetAP2 *in vitro* and the suppression effect of these compounds against tumor-induced angiogenesis *in vivo* (Griffith, et al., (1997) *Chem. Biol. 4*, 461).

Cancer is the second leading cause of death in the U.S., exceeded only by heart disease. Despite recent successes in therapy against some forms of neoplastic disease, other forms continue to be refractory to treatment. Thus, cancer remains a leading cause of death and morbidity in the United States and elsewhere (Bailar and Gornik (1997) *N Engl J Med 336*, 1569). Inhibition of hMetAP2 provides a promising mechanism for the development of novel anti-angiogenic agents in the treatment of cancers.

SUMMARY OF THE INVENTION

In one aspect, the present invention is to a compound of formula (I), or a pharmaceutically active salt thereof, and its use in treating conditions mediated by angiogenesis, such as cancer, haemangioma, proliferative retinopathy, rheumatoid

arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity:



Formula (I)

wherein:

R1 and R2 are, independent from one another, selected from H, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;wherein the C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl may be optionally fused to or substituted by an Ar or Het ring; and

R3 is Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl.

In a second aspect, the present invention is to a method of treating conditions mediated by angiogenesis, such as cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity by administering a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention is to a method of inhibiting MetAP2 in the treatment of angiogenesis-mediated diseases, all in mammals, preferably humans, comprising administering to such mammal in need thereof, a compound of formula (I), or a pharmaceutically active salt thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are used for treating MetAP2-mediated diseases.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted 1,2-aminoalcohols of formula (I) are inhibitors of MetAP2. It has also now been discovered that selective inhibition of MetAP2 enzyme mechanisms by treatment with an inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization and obesity.

The term "C_{1-6}alkyl" as used herein at all occurrences means a substituted and unsubstituted, straight or branched chain radical of 1 to 6 carbon atoms, unless the

chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-6}alkyl group may be optionally substituted independently by one or more of OR^4, R^4, NR^4R^5. C_0alkyl means that no alkyl group is present in the moiety. Thus, Ar-C_0alkyl is equivalent to Ar.

As used herein at all occurrences, substituents R^4, R^5, and R^6 are independently defined as C_{2-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-7}cycloalkyl-C_{0-6}alkyl.

The term "C_{3-7}cycloalkyl" as used herein at all occurrences means substituted or unsubstituted cyclic radicals having 3 to 7 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl radicals.

The term "C_{2-6}alkenyl" as used herein at all occurrences means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included within the scope of this invention. Any C_{2-6}alkenyl group may be optionally substituted independently by one or more of Ph-C_{0-6}alkyl, Het'-C_{0-6} alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}mercaptyl, Ph-C_{0-6}alkoxy, Het'-C_{0-6}alkoxy, OH, NR^4R^5, Het'-S-C_{0-6}alkyl, $(CH_2)_{1-6}OH$, $(CH_2)_{1-6}NR^4R^5$, $O(CH_2)_{1-6}NR^4R^5$, $(CH_2)_{0-6}CO_2R^6$, $O(CH_2)_{1-6}CO_2R^6$, $(CH_2)_{1-6}SO_2$, CF_3, OCF_3 or halogen.

The term "C_{2-6}alkynyl" as used herein at all occurrences means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

The terms "Ar" or "aryl" as used herein interchangeably at all occurrences mean phenyl and naphthyl, optionally substituted by one or more of Ph-C_{0-6}alkyl, Het'-C_{0-6} alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}mercaptyl, Ph-C_{0-6}alkoxy, Het'-C_{0-6}alkoxy, OH, NR^4R^5, Het'-S-C_{0-6}alkyl, $(CH_2)_{1-6}OH$, $(CH_2)_{1-6}NR^4R^5$, $O(CH_2)_{1-6}NR^4R^5$, $(CH_2)_{0-6}CO_2R^6$, $O(CH_2)_{1-6}CO_2R^6$, $(CH_2)_{1-6}SO_2$, CF_3, OCF_3 or halogen; Ph and Het may be optionally substituted with one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}NR^4R^5$, $O(CH_2)_{1-6}NR^4R^5$, CO_2R^6, CF_3, or halogen; two C_{1-6}alkyl or C_{1-6}alkoxy groups may be combined to form a 5-7 membered ring, saturated or unsaturated, fused onto the Ar ring.

The terms "Het" or "heterocyclic" as used herein interchangeably at all occurrences, mean a stable 5- to 7-membered monocyclic, a stable 7- to 10-membered bicyclic, or a stable 11- to 18-membered tricyclic heterocyclic ring all of which are either saturated or unsaturated, and which consist of carbon atoms and from one to

three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}NR^4R^5$, $O(CH_2)_{1-6}NR^4R^5$, CO_2R^6, CF_3, or halogen.

Examples of such heterocycles include, but are not limited to piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridinyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, benzofuranyl, benzothiophenyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl, as well as triazolyl, thiadiazolyl, oxadiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyridazinyl, pyrimidinyl and triazinyl which are available by routine chemical synthesis and are stable.

Het' is defined as for Het and may be optionally substituted by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}NR^4R^5$, $O(CH_2)_{1-6}NR^4R^5$, CO_2R^6, CF_3, or halogen.

The terms "hetero" or "heteroatom" as used herein interchangeably at all occurrences mean oxygen, nitrogen and sulfur.

The "R" group on the secondary amine in the 1,2-aminoalcohol, i.e., R1 and R2, can be defined as: H, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{1-6}-alkyl, or C_{3-7}cycloalkyl.

The terms "halo" or "halogen" as used herein interchangeably at all occurrences mean F, Cl, Br, and I.

Here and throughout this application the term C_0 denotes the absence of the substituent group immediately following; for instance, in the moiety ArC_{0-6}alkyl, when C is 0, the substituent is Ar, e.g., phenyl. Conversely, when the moiety ArC_{0-6}alkyl is identified as a specific aromatic group, e.g., phenyl, it is understood that C is 0.

Suitably, R1 and R2 are, independent from one another, selected from H, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl. Suitably the C_{3-7}cycloalkyl-C_{1-6}-alkyl and C_{3-7}cycloalkyl

substituents may be optionally fused to or substituted by an Ar or Het ring. It will be understood that when R1 and/or R2 are C_{3-7}cycloalkyl-C_{1-6}-alkyl, the point of attachment to the nitrogen may be either the cycloalkyl ring or the C_{1-6}-alkyl chain. Preferably R1 and R2 are independently H and C_{3-7}cycloalkyl, optionally fused to an Ar or Het ring, more preferably C_6cycloalkyl fused to an Ar ring.

Suitably, R3 is Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl. Preferably R3 is Ar-C_{0-6}alkyl, morre preferably Ar, most preferably naphthyl.

Further, it will be understood that when a moiety is "optionally substituted" the moiety may have one or more optional substituents, each optional substituent being independently selected.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be (R), (S) or any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

Among the preferred compounds of the invention are the following compounds:

3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2R)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2R)-2-propanol;

3-(1-Naphthyloxy)-1-cyclohexylamino-(2S)-2-propanol hydrochloride;

3-(1-Naphthyloxy)- 1-[[(1R)- α-methylbenzyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Naphthyloxy)-1-benzylamino-(2S)-2-propanol hydrochloride;

3-(4-Phenylphenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(2-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

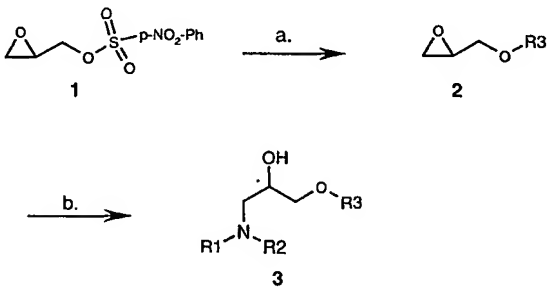
3-(1-Benzyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride; and

3-(1-Phenethyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride.

Methods of Preparation

Compounds of the formula I were prepared according to the procedure outlined in Scheme 1. The sodium alkoxide of an alcohol (such as benzyl, phenethyl, phenyl, 1-naphthyl, 2-naphthyl, and 4-phenyl-phenyl) was heated in the presence of either (2R)-(-)- or (2S)-(+)glycidyl-*p*-NO_2-bezenesulfonate 1-Scheme 1 to afford the glycidyl ether 2-Scheme 1. Treatment of glycidyl ether 2-Scheme 1 with an amine (such as (1R)- or (1S)-1,2,3,4-tetrahydronaphth-1-naphthylamine, (R)-α-methylbenzylamine, benzylamine, cyclohexylamine) under refluxing conditions provided the amino-alcohol 3-Scheme 1.

Scheme 1. Synthesis of (Aryloxy)propanolamines



Reaction Conditions: a.) 1. NaH, DMF, RT, 1 hr
2. R3OH, 100 °C, 2-3 hr b.) R1R2NH, EtOH, 95 °C

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of this invention ("active ingredient") in an amount sufficient to treat cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization or obesity ("MetAp2-mediated disease states") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures

may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of MetAP2-mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must

be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such

administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization or obesity, all in mammals, preferably humans, which comprises administering to such mammal an effective amount of a MetAP2 inhibitor, in particular, a compound of this invention.

By the term "treating" is meant either prophylactic or therapeutic therapy. Such compound can be administered to such mammal in a conventional dosage form prepared by combining the compound of this invention with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The compound is administered to a mammal in need of treatment for cancer, haemangioma, proliferative retinopathy, rheumatoid arthritis, atherosclerotic neovascularization, psoriasis, ocular neovascularization or obesity, in an amount sufficient to decrease symptoms associated with these disease states. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of this invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

EXAMPLES

Example 1

Preparation of 3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthylenyl]amino]-(2S)-2-propanol

a) (2S)-1-Naphthyl glycidyl ether

To a stirring solution of 1-naphthol (1.0 g, 6.93 mmol) in DMF (12 ml) was added 60% sodium hydride in mineral oil (0.27 g, 6.93 mmol) at 0°C. The mixture was then warmed to room temperature, stirred for one hour, and then (2S)-(+)-glycidyl *p*-nitrobenzene sulfonate (1.97 g, 7.63 mmol) was added. The reaction mixture was heated at 100 °C for 3.5 hours and then cooled to room temperature. The mixture reaction mixture was poured into 5% aqueous bicarbonate (60 ml) and extracted four times with EtOAc. The EtOAc extracts were dried over Na_2SO_4, filtered, and concentrated down. The crude mixture was subjected to column chromatography (silica gel, EtOAc/hexane) to provide the title compound as a single stereoisomer as a white solid (0.95 g, 69%). ^{1}H-NMR (400MHz, d6-DMSO) δ•2 .83 (m, 1H), 2.91 (m, 1H), 3.49 (m, 1H), 4.04 (dd, 1H, J=11.4 and 6.2 Hz), 4.51 (dd, 1H, J=11.4 and 2.4 Hz), 6.98 (d, 1H, J=7.2 Hz), 7.41 (t, 1H, J=7.8 Hz), 7.48-7.55 (m, 3H), 7.87 (m, 1H), and 8.18 (m, 1H).

b) 3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthylenyl]amino]-(2S)-2-propanol

To a solution of the compound from Example 1(a) (0.10 g, 0.51 mmol) in ethanol (12 ml) was added (S)-1,2,3,4-tetrahydro-1-naphthyl-amine (90 mg, 0.61 mmol) and the reaction mixture was heated at reflux for 24 hours. The mixture was cooled to room temperature, concentrated down, and subjected to column chromatography (silica gel, MeOH-CH_2Cl_2/EtOAc/hexane) to provide the title compound as a single stereoisomer as a white solid (0.12 g, 71%). ^{1}H-NMR (400MHz, d6-DMSO) δ1.60 (m, 1H), 1.78 (m, 1H), 1.80-2.0 (m, 2H), 2.63-2.78 (m, 3H), 2.91 (m, 1H), 3.71 (m, 1H), 4.04-4.19 (m, 3H), 5.13 (br s, 1H), 6.95 (d, 1H, J=7.3 Hz), 7.02-7.10 (m, 3H), 7.35-7.53 (m, 5H), 7.85 (d, 1H, J=7.7 Hz), and 8.21 (d, 1H, J=7.8 Hz).

Example 2

Preparation of 3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthylenyl]amino]-(2S)-2-propanol

Following the procedure of Example 1(b) except (R)-1,2,3,4-tetrahydro-1-naphthyl-amine was used in step (b) instead of (S)-1,2,3,4-tetrahydro-1-naphthyl-amine, the title compound was prepared as a white solid (85%). ^{1}H-NMR (400MHz,

d6-DMSO) •1.56-1.59 (m, 1H), 1.78 (m, 1H), 1.87-1.90 (m, 2H), 2.60-2.73 (m, 2H), 2.83 (m, 2H), 3.72 (m, 1H), 4.08-4.18 (m, 3H), 5.13 (br s, 1H), 6.96 (d, 1H, J=7.4 Hz), 7.02-7.10 (m, 3H), 7.36-7.53 (m, 5H), 7.85 (d, 1H, J=7.8 Hz), and 8.22 (d, 1H, J=7.9 Hz).

Example 3

Preparation of 3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthylenyl]amino]-(2R)-2-propanol

Following the procedure of Example 1(a)-1(b) except (2R)-(-)-glycidyl *p*-nitrobenzene sulfonate was substituted for (2S)-(+)-glycidyl *p*-nitrobenzene sulfonate in step (a), the title compound was prepared as a white solid (2 steps, 66%). ^{1}H-NMR (400MHz, d6-DMSO) •1.56-1.59 (m, 1H), 1.78 (m, 1H), 1.87-1.90 (m, 2H), 2.60-2.73 (m, 2H), 2.83 (m, 2H), 3.72 (m, 1H), 4.08-4.18 (m, 3H), 5.13 (br s, 1H), 6.96 (d, 1H, J=7.4 Hz), 7.02-7.10 (m, 3H), 7.36-7.53 (m, 5H), 7.85 (d, 1H, J=7.8 Hz), and 8.22 (d, 1H, J=7.9 Hz).

Example 4

Preparation of 3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthylenyl]amino]-(2R)-2-propanol

Following the procedure of Example 1(a)-1(b) except (2R)-(-)-glycidyl *p*-nitrobenzene sulfonate was substituted for (2S)-(+)-glycidyl *p*-nitrobenzene sulfonate in step (a) and (R)-1,2,3,4-tetrahydro-1-naphthyl-amine was used instead of (S)-1,2,3,4-tetrahydro-1-naphthyl-amine in step (b), the title compound was prepared as a white solid (42%). ^{1}H-NMR (400MHz, d6-DMSO) •1.60 (m, 1H), 1.78 (m, 1H), 1.80-2.0 (m, 2H), 2.63-2.78 (m, 3H), 2.91 (m, 1H), 3.71 (m, 1H), 4.04-4.19 (m, 3H), 5.13 (br s, 1H), 6.95 (d, 1H, J=7.3 Hz), 7.02-7.10 (m, 3H), 7.35-7.53 (m, 5H), 7.85 (d, 1H, J=7.7 Hz), and 8.21 (d, 1H, J=7.8 Hz).

Example 5

Preparation of 3-(1-Naphthyloxy)-1-cyclohexylamino-(2S)-2-propanol hydrochloride

Following the procedure of Example 1(a)-1(b) except cyclohexylamine was used in step (b) instead of (S)-1,2,3,4-tetrahydro-1-naphthyl-amine, the desired amine was obtained as a white solid (2 steps, 77%). Hydrogen chloride gas was bubbled into a solution of the amine (70 mg, 0.24 mmol) in 1:1 Et_20/THF (5 ml) for 15 minutes. The mixture was concentrated down and the title compound was prepared as a white solid (100%). ^{1}H-NMR (400MHz, d6-DMSO) •1.10 (m, 1H), 1.21-1.30 (m, 2H), 1.34-1.50 (m, 2H), 1.58 (m, 1H), 1.75-1.80 (m, 2H), 2.09-2.15 (m, 2H), 3.10-3.18 (m,

2H), 3.26-3.35 (m, 1H), 4.15 (d, 2H, J=5.0 Hz), 4.39 (m, 1H), 5.99 (d, 1H, J=4.8 Hz), 6.97 (d, 1H, J=7.5 Hz), 7.42 (t, 1H, J=7.8 Hz), 7.48-7.52 (m, 3H), 7.87 (d, 1H, J=7.1 Hz), 8.25 (d, 1H, J=8.9 Hz), 8.72 (m, 1H), and 9.03 (m, 1H).

Example 6

Preparation of 3-(1-Naphthyloxy)-1-benzylamino-(2S)-2-propanol hydrochloride

Following the procedure of Example 5 except benzylamine was used in instead of cyclohexylamine, the title compound was prepared as a white solid (46%). ^{1}H-NMR (400MHz, d6-DMSO) •3.07-3.10 (m, 1H), 3.22-3.30 (m, 1H), 4.11-4.14 (m, 2H), 4.25 (s, 2H), 4.40 (m, 1H), 6.00 (d, 1H, J=4.9 Hz), 6.95 (d, 1H, J=7.5 Hz), 7.39-7.51 (m, 7H), 7.53-7.60 (m, 2H), 7.87 (d, 1H, J=8.0 Hz), 8.11 (d, 1H, J=8.2 Hz), and 9.3 (m, 1H).

Example 7

Preparation of 3-(1-Naphthyloxy)-1-[[(1R)-α-methylbenzyl]amino]-(2S)-2-propanol hydrochloride

Following the procedure of Example 5 except (1R)-•-me thylbenzyl amine was used in instead of cyclohexylamine, the title compound was prepared as a white solid (87%). ^{1}H-NMR (400MHz, d6-DMSO) •1.66 (d, 3H, J=6.5 Hz), 2.98 (m, 2H), 4.00-4.04 (m, 1H), 4.10-4.14 (m, 1H), 4.36 (m, 1H), 4.47 (m, 1H), 6.00 (br s, 1H), 6.90 (d, 1H, J=7.6 Hz), 7.37 (t, 1H, J=7.9 Hz), 7.43-7.47 (m, 5H), 7.51 (t, 1H, J=7.9 Hz), 7.67 (m, 2H), 7.84 (d, 1H, J=8.0 Hz), 7.91 (d, 1H, J=8.2 Hz), and 9.6 (m, 1H).

Example 8

Preparation of 3-(2-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

a) (2S)-2-Naphthyl glycidyl ether

Following the procedure of Example 1(a) except 2-naphthol was utilized instead of 1-naphthol in step (a), the title compound was prepared as a white solid (65%). ^{1}H-NMR (400MHz, d6-DMSO) •2.76 (m, 1H), 2.88 (t, 1H, J=4.6 Hz), 3.40 (m, 1H), 3.94 (dd, 1H, J=11.2 and 6.6 Hz), 4.45 (dd, 1H, J=11.2 and 2.5 Hz), 7.20 (dd, 1H, J=8.7 and 2.4 Hz), 7.33-7.37 (m, 2H), 7.46 (t, 1H, J=7.4 Hz), and 7.77-7.84 (m, 3H).

b) 3-(2-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]-amino]-(2S)-2-propanol hydrochloride

Following the procedure of Example 1(b) except (2S)-2-naphthyl glycidyl ether was utilized instead of (2S)- 1-naphthyl glycidyl ether and (R)-1,2,3,4-tetrahydro-1-naphthyl-amine was used instead of (S)-1,2,3,4-tetrahydro-1-naphthyl-amine in step

(b), the desired amine was prepared as a white solid (50%). Hydrogen chloride gas was bubbled into a solution of the amine (65 mg, 0.18 mmol) in 1:1 Et_20/THF (3 ml) for 15 minutes. The mixture was concentrated down and the title compound was prepared as a white solid (100%). ^{1}H-NMR (400MHz, d6-DMSO) •1.35 (m, 1H), 1.99-2.14 (m, 1H), 2.14 –2.25 (m, 2H), 2.75-2.80 (m, 1H), 2.81-2.90 (m, 1H), 2.99 (m, 1H), 3.23 (m, 1H), 4.10 (m, 2H), 4.38 (m, 1H), 4.60 (m, 1H), 5.98 (s, 1H), 7.14-7.37 (m, 6H), 7.46 (m, 1H), 7.62 (d, 1H, J=7.5 Hz), 7.82 (m, 3H), and 9.09 (m, 1H).

Example 9

Preparation of 3-(Phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

a) (2S)-Phenyl glycidyl ether

Following the procedure of Example 1(a) except phenol was utilized instead of 1-naphthol in step (a), the title compound was prepared as a white solid (30%). ^{1}H-NMR (400MHz, $CDCl_3$) •2.78 (m, 1H), 2.92 (m, 1H), 3.38 (m, 1H), 3.98 (m, 1H), 4.22 (m, 1H), 6.90-7.02 (m, 3H), and 7.30 (m, 2H).

b) 3-(Phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

Following the procedure of Example 8(b) except (2S)-phenyl glycidyl ether was utilized instead of (2S)-2-naphthyl glycidyl ether, the title compound was prepared as a white solid (50%). ^{1}H-NMR (400MHz, d6-DMSO) •1.73 (m, 1H), 1.99-2.20 (m, 3H), 2.69-2.74 (m, 1H), 2.80-2.85 (m, 1H), 2.93 (m, 1H), 3.17 (m, 1H), 3.96 (m, 2H), 4.31 (m, 1H), 4.59 (m, 1H), 5.94 (s, 1H), 6.92-6.96 (m, 4H), 7.18-7.31 (m, 4H), 7.63 (d, 1H, J=7.6 Hz), and 9.12-9.26 (m, 1H).

Example 10

Preparation of 3-(Benzyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

a) (2S)-Benzyl glycidyl ether

Following the procedure of Example 1(a) except benzyl alcohol was utilized instead of 1-naphthol in step (a), the title compound was prepared as a white solid (30%). ^{1}H-NMR (400MHz, $CDCl_3$) •2.64 (m, 1H), 2.81 (m, 1H), 3.21 (m, 1H), 3.46 (m, 1H), 3.78 (m, 1H), 4.60 (m, 2H), and 7.26-7.40 (m, 5H).

b) 3-(Benzyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

Following the procedure of Example 8(b) except (2S)-benzyl glycidyl ether was utilized instead of (2S)-2-naphthyl glycidyl ether, the title compound was prepared as a

white solid (49%). ^{1}H-NMR (400MHz, d6-DMSO) •1.71 (m, 1H), 1.90-2.20 (m, 3H), 2.73-2.79 (m, 3H), 3.09 (m, 1H), 3.39-3.48 (m, 2H), 4.09 (m, 1H), 4.49 (s, 2H), 4.55 (m, 1H), 5.69 (d, 1H, J=4.8 Hz), 7.18-7.37 (m, 7H), 7.57 (d, 1H, J=7.5 Hz), and 9.03 (m, 2H).

Example 11

Preparation of 3-(Phenethyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

a) (2S)-Phenethyl glycidyl ether

Following the procedure of Example 1(a) except phenethyl alcohol was utilized instead of 1-naphthol in step (a), the title compound was prepared as a white solid (30%). ^{1}H-NMR (400MHz, $CDCl_3$) •2.63 (m, 1H), 2.81 (m, 1H), 2.93 (m, 2H), 3.17 (m, 1H), 3.40-3.55 (m, 1H), 3.69-3.80 (m, 3H), 7.21-7.28 (m, 3H), and 7.28-7.34 (m, 2H).

b) 3-(Phenethyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

Following the procedure of Example 8(b) except (2S)-phenethyl glycidyl ether was utilized instead of (2S)-2-naphthyl glycidyl ether, the title compound was prepared as a white solid (65%). ^{1}H-NMR (400MHz, d6-DMSO) •1.71 (m, 1H), 1.95 (m, 1H), 2.04 (m, 2H), 2.73-2.77 (m, 3H), 2.79 (t, 2H, J=6.7 Hz), 2.99 (m, 1H), 3.35(m, 1H), 3.42-3.45 (m, 1H), 3.61 (t, 2H, J=6.8 Hz), 4.03 (m, 1H), 4.52 (m, 1H), 5.65 (br s, 1H), 7.19-7.32 (m, 8H), 7.56 (m, 1H), and 8.94 (m, 1H).

Example 12

Preparation of 3-(4-Phenyl-phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

a) (2S)-4-Phenyl-phenyl glycidyl ether

Following the procedure of Example 1(a) except 4-phenylphenol was utilized instead of 1-naphthol in step (a), the title compound was prepared as a white solid (36%). ^{1}H-NMR (400MHz, $CDCl_3$) •2.73 (m, 1H), 2.85 (m, 1H), 3.34 (m, 1H), 3.86 (dd, 1H, J=11.2 and 6.3 Hz), 4.87 (d, 1H, 11.4 Hz), 7.03 (d, 2H, J=7.7 Hz), 7.32 (m, 1H), 7.42 (t, 2H, J=7.2 Hz), and 7.59-7.61 (m, 4H).

b) 3-(4-Phenyl-phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride

Following the procedure of Example 8(b) except (2S)-4-phenyl-phenyl glycidyl ether was utilized instead of (2S)-2-naphthyl glycidyl ether, the title compound was prepared as a white solid (78%). ^{1}H-NMR (400MHz, d6-DMSO) •1.75 (m, 1H), 1.98

(m, 1H), 2.12 (m, 2H), 2.75-2.81 (m, 2H), 2.96 (m, 1H), 3.20 (m, 1H), 4.03 (m, 2H), 4.30 (m, 1H), 4.59 (m, 1H), 5.94 (br s, 1H), 7.02 (d, 2H, J=8.3 Hz), 7.19-7.25 (m, 2H), 7.30 (t, 2H, J=7.2 Hz), 7.42 (t, 2H, J=7.5 Hz), 7.59-7.62 (m, 5H), and 9.05 (m, 1H).

Biological Data:

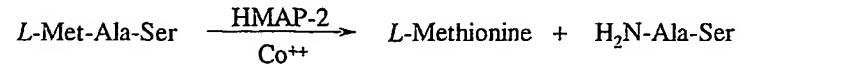
Direct Spectrophotometric Assays of hMetAP2

The hMetAP2 activity can be measured by direct spectrophotometric assay methods using alternative substrates, L-methionine-*p*-nitroanilide (Met-pNA) and L-methionine-7-amido-4-methylcoumarin (Met-AMC). The formation of *p*-nitroaniline (pNA) or 7-amido-4-methylcoumarin (AMC) was continuously monitored by increasing absorbance or fluorescence at 405 nm and 460 nm, respectively, on a corresponding plate reader. All assays were carried out at 30 °C. The fluorescence or spectrophotometric plate reader was calibrated using authentic pNA and AMC from Sigma, respectively. For a typical 96-well plate assay, the increase in the absorbance (at 405 nm for pNA) or the fluorescence emission (λ_{ex} = 360 nm, λ_{em} = 460 nm, for AMC) of a 50 uL assay solution in each well was used to calculate the initial velocity of hMetAP2. Each 50 uL assay solution, contained 50 mM Hepes·Na^+ (pH 7.5), 100 mM NaCl, 10-100nM purified hMetAP2 enzyme, and varying amounts of Met-AMC (in 3% DMSO aqueous solution) or Met-pNA. Assays were initiated with the addition of substrate and the initial rates were corrected for the background rate determined in the absence of hMetAP2.

Coupled Spectrophotometric Assays of hMetAP2

The methionine aminopeptidase activity of hMetAP2 can also be measured spectrophotometrically by monitoring the free L-amino acid formation. The release of N-terminal methionine from a tripeptide (Met-Ala-Ser, Sigma) or a tetrapeptide (Met-Gly-Met-Met, Sigma) substrate was assayed using the L-amino acid oxidase (AAO) / horse radish peroxidase (HRP) couple (eq. 1-3a,b). The formation of hydrogen peroxide (H_2O_2) was continuously monitored at 450nm (absorbance increase of o-Dianisidine (Sigma) upon oxidation, $\Delta\varepsilon$ = 15,300 $M^{-1}cm^{-1}$)2 and 30 °C in a 96- or 384-well plate reader by a method adapted from Tsunasawa, S. et al.(1997) (eq. 3a). Alternatively, formation of H_2O_2 was followed by monitoring the fluorescence emission increase at 587nm ($\Delta\varepsilon$ = 54,000 $M^{-1}cm^{-1}$, λ_{ex} = 563 nm, slit width for both excitation and emission was 1.25 mm) and 30 °C using Amplex Red (Molecular Probes, Inc) (Zhou, M. et al. (1997) *Anal. Biochem. 253*, 162) (eq. 3b). In a total volume of 50 uL, a typical assay contained 50 mM Hepes·Na^+, pH 7.5, 100 mM NaCl, 10 uM $CoCl_2$, 1 mM *o*-Dianisidine or 50 uM Amplex Red, 0.5 units of HRP (Sigma), 0.035 unit of AAO (Sigma), 1 nM hMetAP2, and varying

amounts of peptide substrates. Assays were initiated by the addition of hMetAP2 enzyme, and the rates were corrected for the background rate determined in the absence of hMetAP2.



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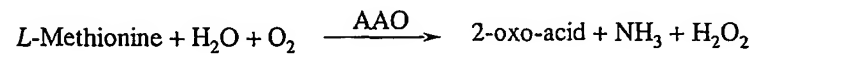

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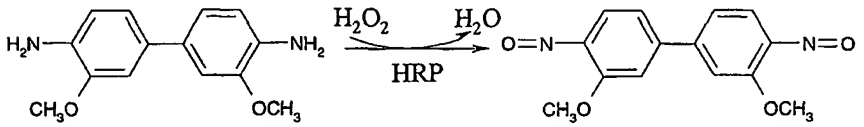
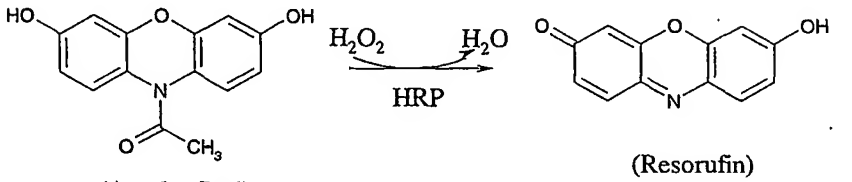


(3a)

(o-Dianisidine)



(3b)

(Amplex Red) (Resorufin)

Kinetic Data Analysis

Data were fitted to the appropriate rate equations using Grafit computer software. Initial velocity data conforming to Michaelis-Menton kinetics were fitted to eq. 4. Inhibition patterns conforming to apparent competitive and non-competitive inhibition were fitted to eq. 5 and eq. 6, respectively.

$$v = VA/(K_a + A) \quad (4)$$

$$v = VA/[K_a(1 + I/K_{is}) + A] \quad (5)$$

$$v = VA/[K_a(1 + I/K_{is}) + A(1 + I/K_{ii})] \quad (6)$$

In eqs 4 - 6, v is the initial velocity, V is the maximum velocity, K_a is the apparent Michaelis constant, I is the inhibitor concentration, and A is the concentration of variable substrates. The nomenclature used in the rate equations for inhibition constants is that of Cleland (1963), in which K_{is} and K_{ii} represent the apparent slope and intercept inhibition constants, respectively.

Cell growth inhibition assays

The ability of MetAP2 inhibitors to inhibit cell growth was assessed by the standard XTT microtitre assay. XTT, a dye sensitive to the pH change of mitochondria in eukaryotic cells, is used to quantify the viability of cells in the presence of chemical compounds. Cells seeded at a given number undergo approximately two divisions on average in the 72 hours of incubation. In the absence of any compound, this population of cells is in exponential growth at the end of the incubation period; the mitochondrial activity of these cells is reflected in the spectrophotometric readout (A_{450}). Viability of a similar cell population in the presence of a given concentration of compound is assessed by comparing the A_{450} reading from the test well with that of the control well. Flat-bottomed 96-well plates are seeded with appropriate numbers of cells (4-6 x 10^3 cells/well in a volume of 200 ul) from trypsinized exponentially growing cultures. In the case of HUVECs, the wells are coated with matrigel prior to establishing the cultures. To "blank" wells is added growth medium only. Cells are incubated overnight to permit attachment. Next day, medium from wells that contain cells is replaced with 180 ul of fresh medium. Appropriate dilutions of test compounds are added to the wells, final DMSO concentration in all wells being 0.2 %. Cells plus compound are incubated for an additional 72 hr at 37°C under the normal growth conditions of the cell line used. Cells are then assayed for viability using standard XTT/PMS (prepared immediately before use: 8 mg XTT (Sigma X-4251) per plate is dissolved in 100 ul DMSO. 3.9 ml H_2O is added to dissolve XTT and 20 ul of PMS stock solution (30 mg/ml) is added from frozen aliquoted stock solution (10 mg of PMS (phenazine methosulfate, Sigma P-9625) in 3.3 ml PBS without cations. These stocks are frozen at -20°C until use). 50 ul of XTT/PMS solution is added to each well and plates incubated for 90 minutes (time required may vary according to cell line, etc.) at 37°C until A_{450} is >1.0. Absorbance at 450 nM is determined using a 96-well UV plate reader. Percent viability of cells in each well is calculated from these data (having been corrected for background absorbance). IC_{50} is that concentration of compound that reduces cell viability to 50% control (untreated) viability.

The compounds of this invention show MetAP2 inhibitor activity having IC_{50} values in the range of 0.0001 to 100 uM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of this invention are inhibitors of MetAP2 and which bind thereto with an IC_{50} value in the range of 0.0001 to 100 uM.

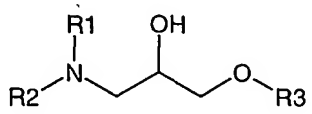
All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were

specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of inhibiting MetAP2 in mammals, comprising administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

R1 and R2 are, independent from one another, selected from H, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;wherein the C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl may be optionally fused to or substituted by an Ar or Het ring; and

R3 is Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl.

2. The method of claim 1, wherein the compound of formula (I) is selected from:

3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2R)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2R)-2-propanol;

3-(1-Naphthyloxy)-1-cyclohexylamino-(2S)-2-propanol hydrochloride;

3-(1-Naphthyloxy)- 1-[[(1R)-• -methylbenzyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Naphthyloxy)-1-benzylamino-(2S)-2-propanol hydrochloride;

3-(4-Phenylphenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

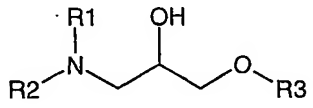
3-(1-Phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(2-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Benzyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride; and

3-(1-Phenethyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride, or a pharmaceutically acceptable salt thereof.

3. A method for treating a disease mediated by MetAP2 in mammals, comprising administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



Formula (I)

wherein:

R1 and R2 are, independent from one another, selected from H, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;wherein the C_{3-7}cycloalkyl-C_{1-6}-alkyl, C_{3-7}cycloalkyl may be optionally fused to or substituted by an Ar or Het ring; and

R3 is Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl.

4. The method of claim 3, wherein the compound of formula (I) is selected from:

3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2R)-2-propanol;

3-(1-Naphthyloxy)-1-[[(1S)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2R)-2-propanol;

3-(1-Naphthyloxy)-1-cyclohexylamino-(2S)-2-propanol hydrochloride;

3-(1-Naphthyloxy)- 1-[[(1R)-• -methylbenzyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Naphthyloxy)-1-benzylamino-(2S)-2-propanol hydrochloride;

3-(4-Phenylphenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Phenoxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(2-Naphthyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride;

3-(1-Benzyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride; and

3-(1-Phenethyloxy)-1-[[(1R)-1,2,3,4-tetrahydro-1-naphthenyl]amino]-(2S)-2-propanol hydrochloride, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/22669

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/135
US CL :514/652

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/652

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS, MED LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 6,207,704 A (LIU et al) 27 March 2001, see entire document.	1-4
A	US 6,242,494 A (CRAIG et al) 05 June 2001, see entire document.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 SEPTEMBER 2001	Date of mailing of the international search report 16 NOV 2001
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